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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/068,507	07/15/1998	VINCENT G. H. EJSINK	1380-122PCT	2387

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EXAMINER

SLOBODYANSKY, ELIZABETH

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 12/31/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/068,507

Applicant(s)

EIJISINK ET AL.

Examiner

Elizabeth Slobodyansky

Art Unit

1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 October 2002.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 69-85,87-107 and 109-125 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 69-85,87-107 and 109-125 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 27, 29.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

Art Unit: 1652

DETAILED ACTION

The amendment filed October 15, 2002 canceling claims 86 and 108, amending claims 69, 70 and 107 and adding claims 109-125 has been entered.

Claims 69-85, 87-107 and 109-125 are pending.

On page 13 of Remarks Applicants state the submission of a revised Sequence Listing. The examiner notes that neither the printed copy of the revised Sequence Listing nor the computer readable form thereof were received in the PTO.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 69-85, 87-107 and 109-125 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 69-85, 87-107 and 109-125 are drawn to or depend from several genera selected from the group of first inducible promoter, an IF gene, a SakK gene, a SakR

Art Unit: 1652

gene, the expression products of said genes and functional analogs thereof from any source or from *Lactobacillus*.

The claims are directed to a genus of IF genes from any source or from *Lactobacillus*. The specification teaches the structure of only a single representative species of such IF genes, the IF gene *Lactobacillus sake* LTH673 encoding SEQ ID NO:3. The second disclosed *Lactobacillus* species, *Lactobacillus plantarum* C11 comprising plnA, plnB, plnC and plnD genes is different from *Lactobacillus sake* LTH673 because the same gene, plnA, encodes both an inducer and a bacteriocin in the plantaricin system whereas the expression product of an IF gene, an inducer, and sakacin P, a bacteriocin, are encoded by different genes. Therefore, it appears that the plantaricin system is more similar to the nisin system than to the sakacin P system.

Thus, the genus of IF genes includes numerous structural variants, and the genus is highly variant because a significant number of structural and functional differences between genus members is permitted. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of being "IF gene".

The claims are further directed to a genus of SakK genes and SakR genes, the expression products of said genes and functional analogs thereof IF genes from any source or from *Lactobacillus*. Claim 125 recites "histidine kinase protein of a *Lactobacillus* species" and "a response regulator protein of a *Lactobacillus* species"

Art Unit: 1652

that are alternative names for the products of a SakK gene and a SakR gene, respectively. The specification teaches a simplified mechanism of function of said genes in *Lactobacillus sake* LTH673 without describing the structure thereof. With regard to *Lactobacillus plantarum* C11 comprising plnA, plnB, plnC and plnD C11, the specification does not teach whether a plnC gene and/or a plnD gene have the same function as the SakR gene. Therefore, SakK genes and SakR genes and their products are described by neither structure nor other identifying characteristics correlated to function.

The claims further recite "a first inducible promoter" that is induced by the expression product of the SakR gene or, in case of claim 109 and the dependent claims, by any compound. Applicants disclose five naturally occurring promoters (Figure 4). They teach the conservative regions 5 to 10 nucleotides long and spaced 17 to 23 nucleotides apart within these sequences (Figure 4). However, the genus of first inducible promoters comprises the naturally-occurring sequence shown at Figure 4 and a great number of man made molecules of unknown length which composition is defined at most by 20 nucleotides. Considering the promoter that is about 80 nucleotides long, the conservative residue represent about 20% of the entire structure. The application teaches that "the product of R acts ion the promoter elements depicted in Fig. 4 either directly, as an activator, or indirectly, by binding to a repressor that untill the moment of induction prevents transcription" (page 19, lines 30-33). The

Art Unit: 1652

specification fails to describe the correlation between the entire promoter structure and its function common to the members of the genus. Therefore, the genus of "a first inducible promoter" is at most described by some structural elements without correlation to function.

Given this lack of an adequate description that identify members of the above genera the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claims 69-85, 87-107 and 109-125 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a gene expression system for genus *Lactobacillus* comprising a promoter inducible by the IF gene expression product, an IF gene, a SakK gene and a SakR gene from LTH673, a kit comprising it and a method of use thereof and for promoter of SEQ ID NOs: 6-10, does not reasonably provide enablement for said expression system suitable for any host and an expression system comprising functional analogs of said elements and a kit and a method of use thereof as well as for a promoter comprising only conservative regions of SEQ ID NOs: 6-10 having unknown homology thereto that is inducible by the product of R gene or by unknown compound. The specification does not enable any person

Art Unit: 1652

skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

This rejection incorporates the rejection made in the previous Office action mailed May 14, 2002. Below is the reworded and more detailed rejection as it applies to amended claim 107 and new claim 109, with dependent claims 120-123.

The claims encompass engineered promoters induced by a SakR gene expression product (claim 107) or an inducer of unknown structure (claim 109). As discussed above, at most only 20% of the promoter structure is defined. Thus, the claims encompass promoters with even low homology to SEQ ID NOs: 6-10. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of nucleotides sequences broadly encompassed by the claims. The specification does not provide a guidance with regard to the rest of the structure and its effect on the promoter's function.

The specification does not support the broad scope of the claims which encompass promoters with even low homology to SEQ ID NOs: 6-10 because the specification does not establish a rational and predictable scheme for modifying nucleotides with an expectation of obtaining the desired biological function and the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Art Unit: 1652

Further, with regard to claim 109, without knowing the inducer, one of ordinary skill in the art would not know how to use a promoter inducible by unknown compound in addition to not knowing how to make it.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and/or the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of nucleotides modifications of any promoter with no or low homology to SEQ ID NOs: 6-10. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of a promoter inducible by a SakR gene product or by an unknown compound is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 69-85, 87-107 and 109-125 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims recite IF, SakK, SakR, plnA, plnB, plnC, etc. The metes and bounds of these terms are indefinite because it is unclear what molecules are encompassed by

Art Unit: 1652

the terms. It further confusing that some claims refer to said genes "of a lactic acid bacterium". It is unclear whether it implies that genes not from lactic acid bacteria are encompassed.

The claims are confusing as reciting a functional analogue. The metes and bounds of this term are not defined in the specification or known in the art.

Claims 120-123 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: at least the SakR gene expression product.

Response to Arguments

Applicant's arguments filed October 15, 2002 have been fully considered but they are not persuasive.

With regard to the written description, Applicants argue that "structural limitations on the promoter are "common structural feature" that serves to define the generic invention" (page 14). This is not persuasive because said "common structural feature" does not constitute a substantial portion of the genus as the remainder of the structure of an inducible promoter is completely undefined. Fragments consisting of about 20 nucleotides are highly unlikely to impart the requisite promoter activity and the

Art Unit: 1652

specification does not define the remaining structural features necessary for members of the genus to be selected.

Applicants further argue that "as the nucleotide sequences of the genes [the SakK and SakR] set forth in the claims were known at the time of filing of the application, it is not necessary that these sequences be set forth in the instant application" (page 14, last paragraph, through page 16, 1st paragraph). This is not agreed with because as an essential material said sequences must be described in the specification.

With regard to the enablement, Applicants argue that it is not undue experimentation to find the functional analogs of the IF, SakK and SakR genes (page 20-22). This is not agreed with because Applicants do not teach features that render the system of the instant invention different from nisin A system and a plantaricin system. NisA and plnA, respectively, encode both an inducer and a bacteriocin whereas the expression product of an IF gene, an inducer, and sakacin P, a bacteriocin, are encoded by different genes. Therefore, it appears that the plantaricin system is more similar to the nisin system than to the sakacin P system. Applicants fail to point out the features of a bacteriocin cluster that impart the ability to produce both an inducing agent and a bacteriocin wherein they are not the same.

Applicants do not argue the 112, 2nd paragraph, rejections.

Art Unit: 1652

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky whose telephone number is (703) 306-3222. The examiner can normally be reached Monday through Friday from 9:30 AM to 6:00 PM.

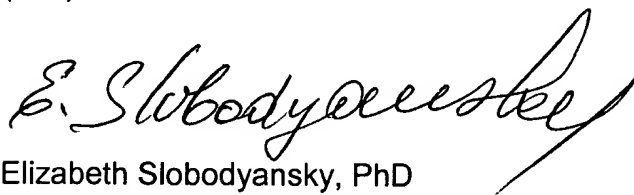
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX phone number for Technology Center 1600 is (703) 308-4242.

Application/Control Number: 09/068,507

Page 11

Art Unit: 1652

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Center receptionist whose telephone number is (703) 308-0196.

A handwritten signature in cursive script, reading "E. Slobodyansky". The signature is written in black ink and is positioned above the printed name and title.

Elizabeth Slobodyansky, PhD
Primary Examiner

December 27, 2002